DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 16 1996

Lilly A. Johnson
4041 Lauri Jo Drive
Marietta, Georgia 30060

Re: Docket No. 78N-0065
Comment No. C23

Dear Miss Johnson:

This is in response to your letter received by the agency on June 24, 1996, regarding skin cream products containing hydroquinone.

Your letter states your frustration with the cream containing 2% hydroquinone. You explained that creams containing a higher percentage of hydroquinone helped you for many years, but that the 2% cream is not working at all. You stated that people should be permitted to use products containing a higher concentration of hydroquinone at their own risk, and compared the situation to the use of cigarettes and alcohol. You further pointed out that many people have adverse reactions to items marketed legally, and removing everything that results in adverse reactions from the market would leave nothing at all available. You also suggested that the labeling could inform people on what to do if adverse reactions should occur.

I am sorry to hear that you are unable to achieve satisfactory results with the presently marketed products. However, taking into consideration the benefit-risk assessment of hydroquinone, based on the information available at this time, higher concentrations of hydroquinone are unlikely. The enclosed Federal Register notice, dated September 3, 1982, discusses our concerns regarding the higher concentration of hydroquinone on pages 39109-39110.

We are planning to have a public meeting before the end of the year to consider additional safety aspects of hydroquinone.

78N-0065

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In addition, we will evaluate all the comments, including yours, in response to the publication, and will publish a final rule at some future date.

I regret that I cannot be more helpful at this time.

Sincerely yours,

Debra L. Bowen, M.D.
Director
Division of OTC Drug Products
Center for Drug Evaluation and Research

Enclosure

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: OCT 16 1996

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 78N-0065

TO: Dockets Management Branch, HFA-305

The attached material should be placed on public display under the above referenced Docket No.

This material should be cross-referenced to Comment No. C23.

Debra L. Bowen, M.D.

Attachment

Federal Register

Friday
September 3, 1982

Part V

Department of Health and Human Services

Food and Drug Administration

Skin Bleaching Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 358

[Docket No. 78N-0065]

Skin Bleaching Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) skin bleaching drug products (products that bleach or otherwise lighten limited areas of brownish skin through suppression of melanin pigment formation within the skin cells) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of Advisory Review Panel on OTC Miscellaneous External Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs on the proposed regulation by November 2, 1982. New data by September 3, 1983. Comments on the new data by November 3, 1983. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the Federal Register of September 29, 1981 (46 FR 47730). Written comments on the agency's economic impact determination by January 3, 1983.

ADDRESS: Written comments, objections, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. New data and comments on new data should also be addressed to the dockets Management Branch.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, National Center for Drugs and Biologics (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the Federal Register of November 3, 1978 (43 FR 51546) FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC skin bleaching drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by February 1, 1979. Reply comments in response to comments filed in the initial comment period could be submitted by March 5, 1979.

In a notice published in the Federal Register of March 21, 1980 (45 FR 18404), the agency advised that it had reopened the administrative record for OTC skin bleaching drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record previously had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980, should be available to the agency in developing a proposed regulation in the form of a tentative final monograph.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened also have been put on display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the Federal Register on November 3, 1978 (43 FR 51546), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulation as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) the FDA states for the first time its position on the establishment of a monograph for OTC skin bleaching drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC skin bleaching drug products.

In response to the advance notice of proposed rulemaking, one drug manufacturers' association and five manufacturers submitted comments. Copies of their comments are on public display in the Dockets Management Branch.

This proposal to establish Part 358 (21 CFR Part 358) constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC skin bleaching drug products, as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

FDA published in the Federal Register of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph (46 FR 47738).

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the Federal Register. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered

for introduction into interstate commerce unless they are the subject of an approved new drug application. Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC skin bleaching drug products (published in the **Federal Register** of November 3, 1978 (43 FR 51546)), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Cateogory II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Skin Bleaching Drug Products

1. One comment stated that the OTC Panel lacked the jurisdiction to make recommendations with respect to cosmetic claims and that the legal standards applicable to cosmetic claims are different from those applicable to drug claims.

The agency agrees that the legal standards applicable to cosmetic claims are different from those applicable to drug claims and that the Panel's jurisdiction extended only to drug claims for skin bleaching products and not to cosmetic claims. The distinction between drug and cosmetic claims is discussed further in comment 18 below.

2. One comment contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464) and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F. 2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F. 2d 887 (2d Cir. 1981).

B. Comments on Hydroquinone

3. One comment requested that the 1.5- to 2-percent hydroquinone concentrations recommended in § 358.10 be increased to concentrations of 1.5 to 4 percent. The comment argued that the Panel itself concluded that the eye damage reported from industrial exposure and the disfiguring skin effects observed after prolonged use of high concentrations and exposure to the sun have not been reported for products containing concentrations under 5 percent hydroquinone. The comment cited several references reviewed by the Panel in support of its argument (Refs. 1 through 5) and stated that 4 percent hydroquinone skin bleaching products have been marketed for years without consumer complaints of any effects of the kind reported from the use of 5 percent or greater concentrations.

The agency has reviewed the available data and agrees with the Panel and the comment that the eye and skin damage cited in the comment have not been reported from use of concentrations of hydroquinone less than 5 percent. However, the agency does not agree with the comment's request to increase the concentration to 4 percent because it has been demonstrated that concentrations of hydroquinone between 2 and 4 percent are not significantly more effective and pose a significantly higher risk of adverse effects. Arndt and Fitzpatrick (Ref. 6) compared 2 and 5 percent hydroquinone cream in 56 patients with hyperpigmented skin. They concluded that the 2-percent cream was as effective but caused less primary irritation than the 5-percent cream.

In a study by Spencer (Ref. 4) cited by the comment in support of the the safety of hydroquinone, derivatives of hydroquinone were used in a clinical study of 142 white and 6 black subjects for a period of 2 months. No significant reactions or sensitization developed using concentrations of 1, 4, or 7 percent. The agency believes that this study cannot be used to support the safety of hydroquinone because it involved derivatives of hydroquinone, not hydroquinone itself. The derivatives of hydroquinone used in the study were the tertiary butyldimethyl ether of hydroquinone and the monotertiary butylmonomethyl ether of hydroquinone.

Significantly, Spencer (Ref. 4) also reported that using 5-percent hydroquinone, alone or in combination with the tertiary butyldimethyl ether of hydroquinone, was effective in a 4-month study of 53 white and 45 black males who completed the study. However, the concentration of 5 percent hydroquinone was reduced to 1.5 and 2 percent after 3 weeks because of contact dermatitis in 33 of the original 122 subjects in the study.

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Spencer (Ref. 5) studied the effects of 2, 3, and 5 percent hydroquinone in 94 white and 43 black men. Although there was only a slight increase in the number of patients in whom depigmentation developed, there was a dramatic increase in the number of inflammatory reactions as the concentrations increased.

With respect to the comment's argument regarding the lack of consumer complaints, the agency believes that market experience alone is not sufficient evidence of safety in light of the available data.

The agency concurs with the Panel that 1.5 to 2 percent hydroquinone is safe and effective for use as a skin bleaching agent when used over limited areas of the body. The agency sees no reason to permit an increase in concentration when the 2-percent concentration is effective because the increased risk of adverse effects likely to occur with concentrations above 2 percent hydroquinone would not be offset by a sufficient proven increase in effectiveness.

References

(1) Stern, G. S., et al., "Further Chronic Toxicity Studies of Hydroquinone," *Federation Proceedings*, 9:121–122, 1950.

(2) Lang, S., N. R. Brewer, and A. J. Carlson, "Chronic Studies of Effect of Hydroquinone on Man," *Federation Proceedings*, 9:74, 1950.

(3) Findlay, G. H., J. G. L. Morrison, and I. W. Simson, "Exogenous Ochronosis and Pigmented Colloid Milium from Hydroquinone Bleaching Cream," *British Journal of Dermatology*, 93:613–622, 1975.

(4) Spencer, M. C., "Hydroquinone Bleaching," *Archives of Dermatology*, 84:131–134, 1961.

(5) Spencer, M. C. "Topical Use of Hydroquinone for Depigmentation," *Journal of the American Medical Association*, 194:962–964, 1965.

(6) Arndt, K. A., and T. B. Fitzpatrick, "Topical Use of Hydroquinone as a Depigmenting Agent," *Journal of the American Medical Association*, 194:965–967, 1965.

4. One comment requested that the monograph for skin bleaching drug products be amended to require that any product containing hydroquinone as a skin bleaching agent contain a stabilizer to retard the oxidation of the hydroquinone and thus maintain the potency of the product.

The agency points out that the Panel recognized that the ease of oxidation of hydroquinone is an important factor in reducing its effectiveness as a skin-lightening agent. The Panel recommended two methods to reduce the oxidation of hydroquinone: (1) Packaging of the product in a small-sized tube (one-half to one ounce) with a small opening to minimize the exposure of the ointment surface to air, or (2) the use of a stabilizing agent such as sodium bisulfite.

The agency does not disagree with the Panel's suggestions for stabilizing hydroquinone products. However, questions relating to the stability of drug products are more appropriately addressed under the regulations for current good manufacturing practice (CGMP) for finished pharmaceuticals in Part 211 (21 CFR Part 211). Under these regulations, marketed drug products are required to meet applicable standards of identity, strength, quality, and purity at the time of use. To insure stability, drug products are required by § 211.137 to bear an expiration date which is determined by appropriate testing described in § 211.166. In the Federal Register of September 29, 1978 (43 FR 45088), FDA proposed a regulation that would grant an exemption from required expiration dating for OTC human drug products that are marketed without dosage limitations and are stable for at least 3 years as supported by appropriate stability data. A final regulation has not been published yet, however. Because hydroquinone skin bleaching products must meet the stability requirements of the CGMP regulations in Part 211, FDA has no objection to the addition of a stabilizer to skin bleaching drug products containing hydroquinone. However, FDA believes that there is no basis in the record to establish in the monograph a requirement that skin bleaching drug products contain a stabilizer.

5. One comment stated that the Panel's statement that "prolonged use of high concentrations (5 percent or more) of hydroquinone with exposure to the sun may produce disfiguring effects" is potentially misleading and should be deleted. The comment argued that the Panel based its statement upon reports of disfiguring effects in a single study by Findlay, Morrison, and Simson (Ref. 1) while a similar study by Arndt and Fitzpatrick (Ref. 2) reported no such effects, even though a 5-percent concentration was used.

The agency agrees with the Panel's view that high concentrations of hydroquinone with exposure to the sun may produce disfiguring effects. This fact was substantiated by Findlay, Morrison, and Simson (Ref. 1), who documented the pathologic changes in 35 cases of hydroquinone damage to the dermis of South African women. Damage followed the prolonged use (2 years and over) of 6 to 8 percent hydroquinone bleaching creams. The Arndt and Fitzpatrick study (Ref. 2) is not comparable to the Findlay, Morrison, and Simson study (Ref. 1) because Arndt and Fitzpatrick used substantially lower concentrations of hydroquinone (2 and 5 percent) and for lesser periods of time (1 to 3 months with treatment discontinued if no effect was seen after 3 months). Additionally, patients were instructed to avoid sunlight. During the summer months patients were advised to use a sunscreen (15 percent aminobenzoic acid) to block the rays of the sun. The agency notes that there is some variance as to the percent of hydroquinone discussed in the Findlay, Morrison, and Simson study (Ref. 1). In one place the study mentions creams "with approximately 5 percent hydroquinone and more," while in another place the authors state that "certain commercial preparations containing 3 percent hydroquinone were strengthened to 6 and 8 percent." In either case the Panel's description of "high concentrations (5 percent or more) of hydroquinone" is not misleading. For these reasons, the agency does not propose to delete this statement.

References

(1) Findlay, G. H., J. G. L. Morrison, and I. W. Simson, "Exogenous Ochronosis and Pigmented Colloid Milium from Hydroquinone Bleaching Cream," *British Journal of Dermatology* 93:613–622, 1975.

(2) Arndt, K. A., and T. B. Fitzpatrick, "Topical Use of Hydroquinone as a Depigmenting Agent," *Journal of the American Medical Association*, 194:965–967, 1965.

C. Labeling Comments

6. One comment objected to the age[redacted]cy's policy of specifying a limited list of terms as the only permissible expressions of indications for use for skin bleaching drug products, specifically only those set forth in § 358.50(b). The comment recommended that § 358.50(b) be revised as follows: *"Indications.* the labeling of the product contains a statement of the indications under the heading 'Indications' making use of one or more of the following phrases, or similar terms conveying substantially the same meaning." The comment argued that as long as a product's indications are accurately described on the labeling, the product cannot be deemed to be misbranded simply because the labeling terms differ from those specifically approved by the Panels.

Since the inception of the OTC drug review, the agency has maintained that a monograph describing the conditions under which an OTC drug will be generally recognized as safe and effective and not misbranded must include both specific active ingredients

and specific labeling. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency has never contended, however, that any list of terms developed during the course of the review literally exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specified time periods or through petitions to amend monographs under 21 CFR 330.10(a)(12). For example, the labeling proposed in this tentative final monograph has been expanded and revised in response to comments received.

During the course of the review, FDA's position on the "exclusivity rule" has been questioned may times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by The Proprietary Association to reconsider its position. To assist the agency in resolving this issue, FDA plans to conduct an open public forum on September 29, 1982 where all interested parties can present their views. The forum will be a legislative type administrative hearing under 21 CFR Part 15 that will be held in response to a request for a hearing on the tentative final monograph for nighttime sleep-aids (published in the **Federal Register** of June 13, 1978; 43 FR 25544). Details of the hearing were announced in a notice published in the **Federal Register** of July 2, 1982 (47 FR 29002). In proposed and tentative final monographs issued in the meantime, the agency will continue to state its longstanding policy.

7. Several comments recommended that the term "skin bleaching" not be used as a statement of identity to describe this class of products because the products do not actully "bleach" the skin. Alternate terms were suggested such as "skin cream," "skin cream which lightens," "medicated skin cream," "skin treatment," "skin toner," "skin color toning," "skin color toner," "lightening brownish skin discolorations," "skin depigmenting agent," "skin lightener," and "bleaching cream."

The agency believes that consumers are familiar with the term "skin bleaching" and that the use of this term along with the indications for the product contained in § 358.50(b) accurately describe for consumers the pharmacologic results to be obtained from using these products. The term "skin lightener" is an allowable alternative for the term "skin bleaching agent" as it accurately describes the expected action of these products. The terms "bleaching cream" and "skin cream which lightens" also adequately describe the identity of a cream product which contains a skin bleaching agent. Because skin bleaching products may not be marketed necessarily in cream formulations but also are marketed in lotion and ointment formulations, the agency will modify these terms to read "skin bleaching (insert dosage form, e.g., cream, lotion or ointment)," or "skin lightening (insert dosage form, e.g., cream, lotion, or ointment)." Section 358.50(a) will be modified to allow the use of any of these terms.

Section 330.10(a)(4)(v) (21 CFR 330.10(a)(4)(v)) states that "Labeling shall be clear and truthful in all respects and * * * shall state the intended uses and results of the product * * *." Accordingly, the agency finds that general terms such as "skin cream," "medicated skin cream," and "skin treatment" are inadequate as a statement of identity because they do not describe the action of the product. Terms such as "skin toner," "skin color toning," and "skin color toner" describe the tinting or shading of skin color or may suggest a direct action on the skin such as improvement in skin elasticity or resiliency, but they fail to describe clearly the pharmacologic action of a skin bleaching agent.

The term "lightening brownish skin discolorations" is a term that best describes an indication and not a statement of identity for skin bleaching products. This term will be addressed under the comments that relate to the labeling indications for skin bleaching products under § 358.50(b). (See comment 8 below.)

The agency proposes that the term "skin depigmenting agent" not be used to identify the intended use of these products because it does not believe that depigmentation is a word that is understood by the ordinary lay consumer under customary conditions of purchase and use. For this reason, the agency also proposes to delete the word "depigmentation" from § 358.50(c)(1)(vi).

8. Several comments requested amending the Panel's recommended indications in § 358.50(b) to include the following: "skin discolorations," "lightening brownish skin discolorations," 'lightens dark pigment in the skin to produce a more even skin tone," "helps produce even tone of the skin," "evens (out) skin tone," "lightens skin tone," "helps achieve an even-toned complexion," "skin color blotches," "for skin that appears blotchy due to uneven pigmentation," "fades dark blotches," "blotches," "blotchy skin," "hand spots," "for fading hyperpigmented areas of the skin," "helps fade away dark spots," and "fades dark areas, or blotches, on the skin." The comments argued that these terms would permit many consumers, particularly Blacks, to understand better the intended action of these products.

The agency does not find the terms "tone" and "hyperpigmented" and the concept of making skin color "even" acceptable for inclusion in the indications for an OTC skin bleaching drug product. Nor does the agency find acceptable any terms that would imply that use of these products should be limited to a particular area of the body, e.g., "hand spots." The word "tone" has a number of meanings, two of which are apt to be confused when applied to products for use on the skin: "color quality or value" and "healthy elasticity" (Ref. 1). The agency believes that substantial confusion can be prevented by excluding the word "tone" from the labeling of a skin bleaching drug product. The word "hyperpigmented" is apt not to be well understood by the majority of consumers, and the agency proposes to use language that is clearer and more meaningful for this purpose. Statements that refer to making skin color "even" are not acceptable because they imply that skin bleaching agents have a selective action on concentrations of pigment and would produce even color if applied indiscriminately to wide areas of skin. In fact, an effective skin bleaching agent would exert its action on all pigment so that the result of indiscriminate application would be a lightening of the color of the total area, not just the portions in which the pigment is concentrated.

In considering the remainder of the language recommended by the Panel and by the comments for use in OTC skin bleaching drug product indications, the agency believes it is important to clarify that these products should be used on skin areas that are brownish in color. Reddish or bluish areas, such as a diffuse port-wine stain or mark, are not amenable to lightening by the use of skin bleaching agents (Ref. 2). The word "brownish" will be added in parentheses after the word "dark," which was recommended by the Panel and which the agency believes may not

be sufficiently specific by itself to assure proper use of the product. So long as a brownish color is specified, the agency finds the words "discolorations," "pigment," "spots," "blotches," and "areas" are acceptable for use in designating appropriate places on the skin to which an OTC skin bleaching agent might be applied. Thus, the indications for OTC skin bleaching products recommended by the Panel is § 358.50(b) (1) and (2) have been combined, revised, and redesignated as § 358.50(b) in the tentative final monograph to read as follows:

Indications. The labeling of the product contains a statement of the indications under the heading "Indications" as follows: (Select one of the following: "For the gradual fading of" or "Lightens") "dark (brownish)" (select one of the following: "discolorations," "pigment," "spots," "blotches," or "areas") "in the skin such as" (select one or more of the following: "freckles," "age and liver spots," or "pigment in the skin that may occur in pregnancy or from the use of oral contraceptives.")

References

(1) "Webster's Collegiate Dictionary," G. and C. Merriam Co., Springfield, MA, 1976, s.v. "tone."

(2) Holvey, D. N., editor, "Hemangiomas," *in* "The Merck Manual," 12th Ed., Merck Sharp and Dohme, Research Laboratories, Rahway, NJ, p. 1483, 1972.

9. Several comments objected to the requirement that the Panel's recommended warning statement in § 358.50(c)(1), "WARNING: Sun exposure should be avoided indefinitely by using a sunscreen agent, a sun blocking agent, or protective clothing to cover bleached skin in order to prevent darkening from reoccurring," be conspicuously boxed and in red letters. The comments argued that this statement merely seeks to caution the consumer of the accelerated reversal of the skin lightening effect resulting from sun exposure and that such information does not justify the prominent display recommended by the Panel. One comment cited section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act and argued that the provisions of this section of the act do not support the warning statement recommended by the Panel because the warning is not necessary for the protection of the public health. Another comment argued that this warning is addressed not to an issue of safety but to one of efficacy. Some comments suggested that the warning be changed to read "to help prevent reversal of the effects of this product, exposure to sunlight should be limited" or "avoid overexposure to sunlight." One comment recommended that the statement be included in the monograph as part of the directions for use rather than as a warning.

The Panel determined, and the agency agrees, that information about the reversal of the hydroquinone skin bleaching effect due to exposure to the sun should be conveyed to consumers. However, repigmentation of the bleached skin by the sun's ultraviolet light is not considered by the agency to be a safety problem, but relates substantially to the effectiveness of the product. Therefore, the agency does not believe that a boxed warning or red letters are necessary to inform the consumer that repigmentation may occur if the area is exposed to the sun.

In addition, the agency agrees with the comments that labeling information should advise the consumer to "limit exposure" or "avoid overexposure" to sunlight and that the best means of achieving this are through the use of a sunscreen agent, a sunblocking agent, or protective clothing. The agency also agrees that it is more appropriate for this information to appear under the directions for use. Accordingly, the agency proposes to incorporate § 358.50(c)(1) from the Panel's recommended monograph into *"Directions"* in § 358.50(d) in the tentative final monograph and modify this statement to read "Sun exposure should be limited by using a sunscreen agent, a sun blocking agent, or protective clothing to cover bleached skin when using and after using this product in order to prevent darkening from reoccurring." For products containing a sunscreen, the statement will be changed slightly to read "Sun exposure should be limited by using a sunscreen agent, a sunblocking agent, or protective clothing to cover bleached skin after treatment is completed in order to prevent darkening from reoccurring." The tentative final monograph does not require that this information be boxed and in red letters.

10. Three comments argued that the warning statement recommended by the Panel in § 358.50(c)(1)(iv), "If no improvement is seen after 2 months of treatment, use of this product should be discontinued," should be deleted or moved to *"Directions"* under § 358.50(d). One comment claimed that the warning was unnecessary because consumers automatically would discontinue use if the product did not work for them. The other comments argued that the Panel had no rationale for the 2-month limitation, and that there was clinical evidence that in some persons it may take up to 3 months before the onset of depigmenting effects (Ref. 1).

The agency agrees that the statement in § 358.50(c)(1)(iv) would be more appropriate as part of the directions for use. The agency also agrees with the comments that the 2-month limitation may not provide sufficient time for some individuals to obtain results and that there is clinical evidence that for some users results are not obtained until after 3 months of use (Ref. 1). Accordingly, the agency proposes that § 358.50(c)(1)(iv) be revised to provide for up to "3 months of treatment" and that it be incorporated into *"Directions"* in § 358.50(d)(1) in the tentative final monograph.

Reference

(1) Arndt, K. A., and T. B., Fitzpatrick, "Topical Use of Hydroquinone as a Depigmenting Agent," *Journal of the American Medical Association*, 194:965–967, 1965.

11. Several comments argued that the Panel had no evidence or rationale to support its recommended limitation of use of hydroquinone for children under 12 years of age in § 358.50(c)(1)(v) and (d)(1). Another comment suggested that it was sufficient that the limitation appear only under *"Directions"* in § 358.50(d)(1) and not under *"Warnings"* in § 358.50(c)(1)(v). One comment suggested that § 358.50(c)(1)(v), "Not recommended for use in children under 12 years of age," be changed to read "Not recommended for use on children under 12 years of age." Another comment suggested that § 358.50(d)(1) be revised to read as follows: "* * * For children under 12, it should only be used on the advice and direction of a physician."

The agency points out that the Panel reviewed the literature and could find no data for either the safety or effectiveness of hydroquinone for use on children under 12 years of age. Because of the absence of data, the Panel could not responsibly conclude that these products were generally recognized as safe and effective for this age group. Based on the indications for these products being proposed in this tentative final monograph, the agency believes that OTC skin bleaching drug products are marketed primarily for adult use. The agency concurs with the Panel that these products should not be used on children under 12 years of age unless a doctor is consulted first.

The agency disagrees that it is sufficient that such a limitation on use appear only under *"Directions"* and not under *"Warnings,"* but believes that this information should be presented in both

sections. The agency agrees with the comments that the word "on" children rather than "in" children should be used in the warning statement and that the warning statement should recognize that the product may be used on the advice and direction of a doctor. Accordingly, the agency proposes that the warning under § 358.50(c) "Not recommended for use in children under 12 years of age" be revised to read as follows: "Do not use on children under 12 years of age unless directed by a doctor." Likewise, the agency proposes that the statement in the *"Directions"* section § 358.50(d)(1)) be revised to read as follows: "Children under 12 years of age: do not use unless directed by a doctor."

12. Several comments requested deletion of the Panel's recommended warning statement in § 358.50(c)(1)(vi) "Depigmentation (lightening) effect of this product may not be noticeable when used on very dark skin." The comments argued that hyerpigmented patches (blotches) are the type of skin most susceptible to treatment with hydroquinone and that hydroquinone showed noticeable changes when used on the dark skin of pigs and on pigmented cells of transplantable mouse melanomas (Refs. 1 and 2).

The agency notes that the data referenced by the comments are supportive of the lightening effects of hydroquinone in certain animal models (Refs. 1 and 2). Nevertheless, the agency agrees with the Panel that there are ample clinical data to conclude that the lightening effect of hydroquinone in humans may not be noticeable when used on very dark skin, and that lighter-skinned individuals are more likely to experience a greater skin-lightening effect (Refs. 3, 4, and 5). However, the agency believes that this information more appropriately is presented under the directions for use. Accordingly, the agency proposes that the information recommended by the Panel in § 358.50(c)(1)(vi) be incorporated in § 358.50(d)(1) in the tentative final monograph. As discussed in comment 7 above, the word "depigmentation" has been deleted because it may not be well understood by the majority of consumers under customary conditions of purchase and use.

References

(1) "An Evaluation of a Cosmetic Cream Containing 2% W/W of Hydroquinone as an Agent for Reducing the Darkness of Black Skin," draft of unpublished report attached to Comment No. C00002, Docket No. 78N-0065, Dockets Management Branch.

(2) Hu, F., "The Influence of Certain Hormones and Chemicals on Mammalian Pigment Cells," *Journal of Investigative Dermatology*, 46:177–124, 1966.

(3) Arndt, K. A., and T. B. Fitzpatrick, "Topical Use of Hydroquinone as a Depigmenting Agent," *Journal of the American Medical Association*, 194:965–967, 1965.

(4) Spencer, M. C., "Topical Use of Hydroquinone for Depigmentation," *Journal of the American Medical Association*, 194:962–964, 1965.

(5) Spencer, M. C., "Hydroquinone Bleaching," *Archives of Dermatology*, 84:131–134, 1961.

13. Several comments recommended changing the directions in § 358.50(d) to make them better understood and more easily followed by lay consumers. They recommended changing "adult topical dosage is the thin application of a 1.5 to 2.0 percent preparation to the affected area twice daily" to read "for adults, apply twice daily to the affected areas or use as directed by a physician."

The agency notes the original wording of the directions for use contained the allowable concentration of hydroquinone. However, it is not likely that the Panels intended the exact wording in this section to be used in labeling as it was not contained in quotation marks in the advance notice of proposed rulemaking. Moreover, FDA believes that stating the concentration of hydroquinone in the directions is unnecessary and might unintentionally confuse the consumer. Because of the hydroquinone concentration is stated in § 358.10, the agency proposes to delete it from § 358.50(d) and reword this section in the tentative final monograph to read, "Adults: apply a small amount as a thin layer on the affected area twice daily, or use as directed by a doctor."

14. One comment requested that the term "Caution" replace the term "Warning" in the preface to the statement in § 358.50(c)(1)(ii), "Avoid contact with eyes." The comment argued that this statement was more appropriately classified as a "caution" rather than as a "warning."

The agency notes that historically there has not been a consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in § § 369.20 and 369.21 (21 CFR 369.20 and 369.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances, either of these signal words is used to convey the same or similar precautionary information.

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. Therefore, FDA has determined that the signal word "warning," rather than the work "caution," will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems.

15. One comment recommended changing the warning in § 358.50(c)(1)(iii) from "If skin irritation develops, use of this product should be discontinued or a physician should be consulted," to "If skin irritation persists, discontinue use or consult a physician." The comment argued that the Panel's recommended warning seemed inconsistent with the observations or Arndt and Fitzpatrick (Ref. 1) who observed, "The occurrence of inflammation makes subsequent lightening more likely."

The agency recognizes that the use of hydroquinone products may be accompanied by a mild inflammatory reaction after the first few weeks of treatment and that this inflammation makes subsequent lightening more likely. In some instances the reaction may be so mild as to go unnoticed. The agency believes that consumers should be advised that a mild skin irritation is expected, but if severe irritation occurs, use of the product should be discontinued. Accordingly, the agency proposes that the warning in § 358.50(c)(1)(iii) (which has been redesignated § 358.50(c)(1)(ii) in this tentative final monograph) be revised as follows: "Some users of this product may experience a mild skin irritation. If skin irritation becomes severe, stop use and consult a doctor."

Reference

(1) Arndt, K. A., and T. B. Fitzpatrick, "Topical Use of Hydroquinone as a Depigmenting Agent," *Journal of the American Medical Association*, 194:965–967, 1965.

16. One comment asked whether the monograph would require labeling that would include a statement that patch testing should precede the use of hydroquinone-containing skin bleaching products. The comment pointed out the Panel's statement at 43 FR 51550 that "the use of hydroquinone for depigmenting * * * should never be considered without a cautious therapeutic trial on a limited, inconspicuous area" (patch testing). The comment questioned whether the absence of a patch-testing requirement in the Panel's recommended monograph indicated that 1.5 and 2 percent hydroquinone preparations do not

present sufficient risk of sensitivity reactions to justify patch-testing labeling. The comment requested the agency to resolve this uncertainty by not requiring patch-testing labeling under the monograph.

The agency believes that the comment misinterpreted the Panel's recommendation as to when a patch test should be employed. In making the statement quoted above by the comment, the Panel was advising that the use of hydroquinone for depigmenting certain conditions, i.e., photosensitization reactions, lichen planus (an inflammatory skin disease), or dermatitis caused by reaction to drugs, never should be considered without a cautious trial (patch testing). The agency believes that the Panel did not mean to imply by this statement that patch testing should be done for normal conditions of use of hydroquinone skin bleaching products.

The agency does not believe that labeling that suggests the consumer perform a patch test before using a skin bleaching product is justified for 1.5 to 2 percent hydroquinone preparations. These preparations are for use only on limited areas of the body. Moreover, this restricted use has not been shown to produce a significant risk of sensitivity reactions when directions for use of the product are followed. Sensitivity reaction normally does not occur at the 2-percent concentration. Accordingly, the agency will not propose patch-testing labeling for 1.5 to 2 percent hydroquinone skin bleaching drug products. Further, the agency believes the skin irritation warning in § 358.50(c)(1)(ii) in the tentative final monograph adequately informs the consumer what course of action to take should sensitization occur. (See comment 15 above.)

17. One comment suggested that an effort be made to limit the number of warnings in § 358.50(c). The comment felt that a minimum of concern for safe use exists with hydroquinone products and, therefore, to promote effective communication with the consumer an effort should be made to limit unnecessary warnings.

The agency has reviewed the warnings recommended by the Panel in § 358.50(c) and proposes that the information contained in three of these warnings be placed under *Directions*. Thus, the agency proposes to reduce the number of warnings from six to three. (See comments 9, 10, and 12 above.)

18. Two comments urged that the Category II labeling section be modified so as not to prohibit cosmetic claims and that a distinction be made between cosmetic claims and drug claims. One of the comments asked that a distinction be drawn between claims that use of skin bleaching products results in healthier, younger, or rejuvenated skin (which are drug claims) and claims that use of the products results in healthier or younger *looking* skin (which are cosmetic claims and should not be prohibited). The comment added that skin bleaching products are used essentially for cosmetic purposes (to achieve visual effects) and that these products are best judged by the consumer's perception of whether the depigmenting effects promote attractiveness. The second comment argued that since these products are used by consumers to improve the appearance of the skin, cosmetic claims which merely refer to this effect should not be proscribed as Category II.

The agency agrees with the comments that a distinction between drug and cosmetic claims must be made because OTC drug monographs contain labeling requirements only for the drug use of products. The Panel recommended that the following kinds of claims be regarded as Category II: claims that are unsupported by scientific data and beyond the known pharmacologic properties of hydroquinone; claims that are not clinically defined or which would imply use of the product on injured skin or burns; claims that use poorly defined terms that would confuse the consumer because the words have a different significance for different people; claims that imply through use of certain terms an immediate rather than a gradual skin bleaching effect; and claims that in any way negate, detract, or deemphasize the warning statements in the labeling. The agency generally agrees with the Panel's recommendations, but does not agree with all of the examples provided by the Panel at 43 FR 51554, for example, "natural aging," which is discussed in comment 19 below, and "blotches," which are discussed in comment 8 above.

While the monograph for skin bleaching products does not include domestic labeling of skin bleaching products, the agency has no objection to cosmetic labeling appearing on these products along with the required drug labeling. Cosmetic claims that refer to improving the appearance of the skin or to more attractive or beautiful skin are acceptable provided they conform to the cosmetic labeling requirements of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 362). Consistent with the provisions of § 701.3(d) (21 CFR 701.3(d)) regarding declaration in labeling of active drug ingredients and cosmetic ingredients, it is the agency's view that cosmetic claims appearing in any portion of the labeling that is required by the monograph could be misleading. Cosmetic claims may appear elsewhere on the label.

19. One comment requested clarification of the Panel's placement in Category II of claims such as "* * * where skin has become discolored, spotted, or darkened from bad weather or natural aging," while it placed claims for "age spots, liver spots, freckles, and melasma" in Category I. The comment argued that the Category II claim might serve as a basis for prohibiting the Category I claim and stated that it was unlikely that this was the Panel's intent.

The agency points out that the claim "for stubborn cases where skin has become discolored, spotted, or darkened from bad weather or natural aging," which was placed in Category II by the Panel, was cited as an example of a claim that is not clinically defined or that would imply use of the skin bleaching product on injured skin or burns. In reviewing this claim, the agency concludes that only that portion of the claim dealing with bad weather would imply that a skin bleaching product was for use on injured skin or burns. The natural aging referred to in the claim very likely could be confused with age and livers spots, for which a skin bleaching product may be used safely. The agency therefore proposes to remove from Category II that portion of the above claim that reads, "or natural aging." The Category I labeling indications for skin bleaching drug products are discussed in comment 8 above.

D. Comments on Combination Products

20. One comment recommended that § 358.20 be expanded to include hydroquinone formulations in a base that is opaque to ultraviolet radiation. The comment specifically mentioned a hydrophilic opaque base containing 10 percent talc as a light-scattering and reflecting agent. The comment included data to illustrate the Sun Protection Factor (SPF) values of its hydroquinone 2 and 4 percent formulations in this base (Ref. 1).

The agency notes that the Panel found hydroquinone combined with a sunscreen to be a rational combination and therefore recommended in § 358.20 that hydroquinone be combined with any generally recognized safe and effective sunscreen active ingredient identified in 21 CFR 352.10 (see the Federal Register of August 25, 1978; 43 FR 38206) provided that the product is labeled only as a skin bleaching agent and not as a sunscreen. The agency

points out that many different ingredients have been recommended in § 352.10 as Category I sunscreens. However, talc is not one of the ingredients listed in § 352.10 and therefore is not presently a Category I sunscreen active ingredient. The agency believes that the sunscreen rulemaking and not the skin bleaching rulemaking is the proper forum in which to consider talc for sunscreen use.

Reference

(1) Comment No. C00007, Docket No. 78N-0065, Dockets Management Branch.

21. One comment requested that the phrase "provided that the product is labeled only as identified in § 358.50" be deleted from § 358.20, which would have permitted combinations of hydroquinone with any generally recognized safe and effective sunscreen active ingredient provided that the product is labeled only as a skin bleaching drug product. The comment argued that the phrase could possibly be interpreted to mean that nonmedical claims, which are permitted on products that contain hydroquinone alone, may not likewise be permitted on products that contain both hydroquinone and a sunscreen.

The agency emphasizes that OTC drug monographs contain appropriate drug labeling claims to be used on OTC drug products and do not preclude the use of acceptable cosmetic claims if the product is both a drug and a cosmetic. The phrase that the comment requested be deleted was intended to relate only to the drug aspects of skin bleaching-sunscreen combination products and was not intended to preclude the use of cosmetic claims.

22. One comment argued that the warning under § 358.50(c)(1), "WARNING: Sun exposure should be avoided indefinitely by using a sunscreen agent, a sun blocking agent, or protective clothing to cover bleached skin in order to prevent darkening from reoccurring," is inconsistent because the warning fails to differentiate between single ingredient hydroquinone products and products containing hydroquinone combined with sunscreen agents. The comment argued that formulations including a sunscreen or sun blocking agent already satisfy the requirement of avoidance of sun exposure by the use of a sunscreen, and the warning statement should not be required on hydroquinone-sunscreen combination drug products.

In its review of hydroquinone and hydroquinone-sunscreen combinations, the Panel recognized that the inclusion of a sunscreen in a hydroquinone-sunscreen combination drug product was not sufficient to forestall the reoccurrence of darkening of the skin by sunlight. The Panel recognized that incorporating a sunscreen in a hydroquinone product would be beneficial only as long as the sunscreen was present on the surface of the skin. When the sunscreen was washed off, or when the consumer stopped using the combination product, the consumer still would be confronted with the problem of reoccurrence of skin darkening when the treated area was exposed to sunlight. Accordingly, the Panel advised that continual protection of the bleached area was necessary regardless of whether hydroquinone was used alone or whether a hydroquinone-sunscreen combination drug product was used. The agency concurs, but believes that consumers should be informed of the difference between products containing a sunscreen and those not containing a sunscreen. As discussed in comment 9 above, this information will now be included in the monograph as part of the directions for use rather than as a warning.

23. One comment requested that § 358.20 and § 358.50 be revised to allow hydroquinone-sunscreen combination products to bear a labeling statement indicating that the product contains an effective sunscreen agent to minimize the effect of sunlight in reversing the skin bleaching effect of hydroquinone.

Two comments requested deletion of the warning for hydroquinone-sunscreen combination products in § 358.50(c)(2), i.e., "This product will bleach skin and is not for use for the prevention of sunburn." The comments reasoned that the absence of a sunburn prevention claim for these products would limit their use as sunburn preventatives, and thus a statement not to use the product for the prevention of sunburn was unwarranted.

Although the Panel found the combination of hydroquinone and a sunscreen rational, it did not provide sufficient information regarding the labeling of such a combination. The Panel recommended that such combination products not be labeled as sunscreens in order to avoid specific reference to their use in preventing sunburn and permitting tanning. The agency agrees but believes that consumers should be informed that the combination product "contains a sunscreen to help prevent darkening from reoccurring". The agency therefore is proposing to include this language in the "Indications" section in this tentative final monograph at § 358.50(b)(2). Because the term "sunscreen" is proposed for inclusion in the labeling, it is especially important to inform consumers that these products are not for the prevention of sunburn. The Panel recommended at § 358(c)(2) the warning, "This product will bleach skin and is not for use for the prevention of sunburn." The agency concurs with the intent of the warning, but proposes to shorten it in the tentative final monograph to read "This product is not for use in the prevention of sunburn."

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions.

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and concurs with the Panel's categorization of hydroquinone in concentrations of 1.5 to 2.0 percent in Category I and ammoniated mercury in Category II. The Panel placed ammoniated mercury in Category II because it felt that ammonitated mercury is not safe for OTC use. Mercury can pass through the skin, especially in an ointment base, and chronic application can cause systemic mercury intoxication. In addition, the Panel was unable to locate data relevent to the efficacy of ammoniated mercury in OTC skin bleaching drug products. (See 43 FR 51553.) The Panel placed no skin bleaching agents in Category III as single ingredients, and the agency concurs.

The recommended monograph reflected the Panel's view that hydroquinone may be combined with any generally recognized safe and effective sunscreen active ingredient. The agency concurs but is proposing revised labeling for all such combinations in the tentative final monograph.

2. *Testing of Category II and Category III conditions.* Because the Panel did not place any ingredients in Category III, it did not recommend any testing guidelines for Category III skin bleaching conditions. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any skin bleaching ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the Federal Register of September 29, 1981 (46 FR 47740). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and

agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations.

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made in the Panel's conclusions and recommendations follows.

1. The agency proposes to add to the Panel's statement of identity ("skin bleaching agent") in § 358.50(a) the alternative trems "skin lightener," "skin bleaching (insert dosage form, e.g., cream, lotion, or ointment)," and "skin lightening (insert dosage form, e.g., cream, lotion, or ointment)." (See comment 7 above.)

2. The agency proposes to combine and revise the Panel's recommended indications in § 358.50(b)(1) and (2) (redesignated § 358.50(b)] to read as follows in the tentative final monograph:

(Select one of the following: "For the gradual fading of" or "Lightens") "dark (brownish)" (select one of the following: "discolorations," "pigment," "spots," "blotches," or "areas") "in the skin such as" (select one or more of the following: "freckles," "age and liver spots," or "pigment in the skin that may occur in pregnancy or from the use of oral contraceptives.") (See comment 8 above.)

3. The warning in § 358.50(c)(1)(iii), "If skin irritation develops, use of this product should be discontinued or a physician should be consulted," has been tentatively redesignated § 358.50(c)(1)(ii) and revised as follows: "Some users of this product may experience a mild skin irritation. If skin irritation becomes severe, stop use and consult a doctor." (See comment 15 above.)

4. The agency proposes to reword the information in the Panel's warnings in § 358.50(c)(1)(i), (iv), and (vi) and move this information to the *"Directions"* in § 358.50(d)(1). This includes information to the effect that sun exposure should be limited by using a sunscreen agent, a sun blocking agent, or protective clothing to cover bleached skin when using and after using the product in order to prevent darkening from reoccurring; a statement that the lightening effect of hydroquinone may not be noticeable on very dark skin; and a statement specifying a use limitation period. (See comments 9, 10, and 12 above.)

5. In light of evidence that for some users 3 months are required in order to obtain results, the agency proposes to increase the 2-month use limitation in § 358.50(c)(1)(iv) to 3 months and to incorporate this limitation in § 358.50(d)(1) as part of the *"Directions."* Further, the agency proposes to delete the concentration of hydroquinone from the *"Directions"* recommended by the Panel in § 358.50(d)(1) as being unnecessary and possibly confusing to consumers. The proposed allowable concentration is included in § 358.10 in the tentative final monogaph. (See comments 10 and 13 above.)

6. The agency has proposed revised labeling for the combination of a skin bleaching agent with a sunscreen. (See comments 22 and 23 above.)

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a Regulatory Impact Analysis, as specified in Executive Order 12291, or a Regulatory Flexibility Analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96-354). Specifically, it would place hydroquinone, the main ingredient used in these products, in Category I, and ammoniated mercury in Category II, as recommended by the Panel. Minimal reformulation and some relabeling would be necessary; however the agency has expanded the labeling recommended by the Panel, so that manufacturers would have a wide choice of language which could be incorporated into their labels at minimal cost in the normal course of reordering. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12291. Further, the agency certifies that the proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities, as defined in the Regulatory Flexibility Act.

The agency invites public comments regarding any substantial or significant economic impact that this rulemaking would have on OTC skin bleaching drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC skin bleaching drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on skin bleaching drug products, a period of 120 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(d)(9) (proposed in the Federal Register of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 358

Over-the-counter drugs, Skin bleaching agents, Wart removers, Nailbiting and thumbsucking deterrents, Ingrown toenail relief.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 358, to read as follows:

PART 358—MISCELLANEOUS EXTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—Skin Bleaching Drug Products

General Provisions

Active Ingredient

Labeling

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—Skin Bleaching Drug Products

General Provisions

§ 358.1 Scope.

(a) An over-the-counter skin bleaching drug product in a form suitable for

topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart in addition to each of the general conditions established in § 330.1.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 358.3 Definition.

As used in this subpart:

Skin bleaching active ingredient. An agent designed to bleach or otherwise lighten limited areas of hyperpigmented skin through the suppression of melanin pigment formation within skin cells.

Active Ingredient

§ 358.10 Skin bleaching active ingredient.

The active ingredient and its concentration in the product is as follows: hydroquinone 1.5 to 2.0 percent.

§ 358.20 Permitted combinations of active ingredients.

Hydroquinone identified in § 358.10 may be combined with any generally recognized safe and effective sunscreen active ingredient identified in § 352.10 provided that the product is labeled according to § 358.50.

Labeling

§ 358.50 Labeling of skin bleaching drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "skin bleaching agent," "skin lightener," "skin bleaching (insert dosage form, e.g., cream, lotion, or ointment)," or "skin lightening (insert dosage form, e.g. cream, lotion, or ointment)."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following phrases:

(1) *For products containing the ingredient identified in § 358.10 or any combination identified in § 358.20.* (Select one of the following: "For the gradual fading of" or "Lightens") "dark (brownish)" (select one of the following: "discolorations," "pigment," "spots," "blotches," or "areas") "in the skin such as" (select one or more of the following: "freckles," "age and liver spots," or "pigment in the skin that may occur in pregnancy or from the use of oral contraceptives.")

(2) *For products containing any combination identified in § 358.20.* "Contains a sunscreen to help prevent darkening from reoccurring."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing the ingredient identified in § 358.10 or any combination identified in § 358.20.*

(i) "Avoid contact with eyes."

(ii) "Some users of this product may experience a mild skin irritation. If skin irritation becomes severe, stop use and consult a doctor."

(iii) "Do not use on children under 12 years of age unless directed by a doctor."

(2) *For products containing any combination identified in § 358.20.* "This product is not for use in the prevention of sunburn."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions":

(1) *For products containing the ingredient identified in § 358.10 or any combination identified in § 358.20.* "Adults: apply a small amount as a thin layer on the affected area twice daily, or use as directed by a doctor. If no improvement is seen after 3 months of treatment, use of this product should be discontinued. Lightening effect of this product may not be noticeable when used on very dark skin.

"Children under 12 years of age: do not use unless directed by a doctor."

(2) *For products containing the ingredient identified in § 352.10.* "Sun exposure should be limited by using a sunscreen agent, a sun blocking agent, or protective clothing to cover bleached skin when using and after using this product in order to prevent darkening from reoccurring."

(3) *For products containing any combination identified in § 358.20.* "Sun exposure should be limited by using a sunscreen agent, a sun blocking agent, or protective clothing to cover bleached skin after treatment is completed in order to prevent darkening from reoccurring."

Interested persons may, on or before November 2, 1982 submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before January 3, 1983. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before September 3, 1983, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before November 3, 1983. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on November 3, 1983. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register** unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Dated: August 9, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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